STUDY OF MITRAL ANNULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE

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CERTIFICATE

This is to certify that this dissertation titled **'MITRAL ANNULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE'** submitted by **Dr. BINJO . J. VAZHAPPILLY** to the faculty of General Medicine, **The Tamilnadu Dr. M.G.R. Medical University, Chennai** in partial fulfillment of the requirement for the award of MD degree branch I General Medicine, is a bonafide research work carried out by him under our direct supervision and guidance.

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This is submitted to **The Tamilnadu Dr. M.G.R. Medical University, Chennai,** in partial fulfillment of the rules and regulations for the award of MD degree (branch I) General Medicine.

Place: Madurai

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CONTENTS

INTRODUCTION

Chronic kidney disease (CKD) is becoming a major public health problem worldwide. The median prevalence of CKD was 7.2% in persons aged 30 years or older. In persons aged 64 years or older prevalence of CKD varied from 23.4% to 35.8%[1]. The prevalence of CKD in India is 0.8%, and diabetes has emerged as the most frequent cause (30–40%)[2] .It is estimated that 1,00,000 new patients of end stage renal disease (ESRD) enter renal replacement programs annually in India[3] .

Chronic kidney disease (CKD) is associated with a high incidence of cardiovascular events.[4] Cardiovascular calcium deposition has been recognized as a common finding in patients with renal failure.[5] .

Mitral annular calcification is a chronic, degenerative process of the mitral valve fibrous ring, involving the posterior annulus. It is a common disorder in the elderly, above all in women. It may also occur in younger patients with advanced renal disease or other metabolic disorders that result in abnormal calcium metabolism. CKD patients are exposed to a much greater risk for the calcification of cardiac valves and coronary arteries than the general

population.[6,7] MAC occurs earlier in patients with chronic renal failure than those without renal dysfunction Mitral annulus calcification in the elderly is associated with a doubled risk of stroke, independent of the traditional risk factors. Each 1 mm increase in mitral annular calcification was associated with an increase in all-cause mortality of about 10 percent.

REVIEW OF LITERATURE

CHRONIC KIDNEY DISEASE

CKD is defined as kidney damage with or without decreased GFR, manifested as either pathologic abnormalities or markers of kidney damage, including abnormalities in composition of blood or urine, abnormality in renal imaging findings and a GFR less than 60 mL/min 1.73 m^2 [8]. The prevalence and the incidence of CKD are increasing. The most common causes of CKD leading to ESRD are diabetes mellitus, hypertension, glomerulonephritis, and cystic kidney disease, which together account for 90% of all new cases of CKD. Hypertensive nephropathy is a common cause of CKD in the elderly. Progressive nephrosclerosis from vascular disease is the renal correlate of the same processes that lead to coronary heart disease and cerebrovascular disease.

The increasing incidence of CKD in the elderly has been ascribed, to decreased mortality from the cardiac and cerebral complications of atherosclerotic vascular disease in them, enabling a greater segment of the population to manifest the renal component of generalized vascular disease. Majority of those

with early stages of renal disease, especially of vascular origin, will succumb to the cardiovascular and cerebrovascular consequences of the vascular disease before they can progress to the most advanced stages of CKD. Inter-individual variability in the rate of progression to CKD has an important heritable component, and a number of genetic loci that contribute to the progression of CKD have been identified. Similarly, it has been noted that women of reproductive age are relatively protected against progression of many renal diseases, and sex-specific responses to angiotensin II and its blockade have been identified.

Pathophysiology of CKD

It involves two broad sets of mechanisms of damage: (1) initiating mechanisms specific to underlying etiology like immune complexes and mediators of inflammation in glomerulonephritis, or toxins in certain diseases of the renal tubules and interstitium; and

(2) a set of progressive mechanisms, involving hyperfiltration and hypertrophy of the remaining viable nephrons, that are a common consequence following long-term reduction of renal mass. Increased intrarenal activity of the renin-angiotensin axis appears to contribute

both to the initial adaptive hyperfiltration and to the subsequent maladaptive hypertrophy and sclerosis.

Risk Factors for Chronic Kidney Disease

Established risk factors
Age Gender (male predilection) Race (African American, Native American) High blood pressure Diabetes mellitus Obesity Metabolic syndrome Proteinuria Family history of kidney disease Smoking Atherosclerosis Exposure to nephrotoxins such as analgesics, heavy metals Dyslipidemia Reduced nephron number at birth Recurrent urinary tract infection
Emerging risk factors
Oxidative stress Elevated plasma homocysteine level Anemia Prothrombotic factors (e.g., plasminogen inhibitor activator-1)

CAUSES OF CHRONIC RENAL FAILURE [9]

Diabetic glomerulosclerosis

Hypertensive nephrosclerosis

Glomerular disease

- Glomerulonephritis
- Amyloidosis, light chain disease
- Systemic lupus erythematosus, Wegener's granulomatosis

Tubulointerstitial disease

- Reflux nephropathy (chronic pyelonephritis)
- Analgesic nephropathy
- Obstructive nephropathy (stones, benign prostatic hypertrophy)
- Myeloma kidney

Vascular disease

- Scleroderma
- Vasculitis
- Renovascular renal failure (ischemic nephropathy)
- Atheroembolic renal disease

Cystic diseases

- Autosomal dominant polycystic kidney disease
- Medullary cystic kidney disease

STAGES OF CKD WITH THE FREQUENCY OF COMPLICATIONS

Stage	Description	GFR(mL/min/1.73 m^2)	Symptoms or Signs
1	Chronic kidney damage with normal or increased GFR	>90	Anemia 4%
			Hypertension 40%
			5-year mortality 19%
2	Mild GFR loss	60–89	Anemia 4%
			Hypertension 40%
			5-year mortality 19%
3	Moderate GFR loss	30–59	Anemia 7%
			Hypertension 55%
			5-year mortality 24%
4	Severe GFR loss	15–29	Hyperphosphatemia 20%
			Anemia 29%
			Hypertension 77%
			5-year mortality 46%
5	Kidney failure ESRD	<15 or dialysis	Hyperphosphatemia 50%
			Anemia 69%
			Hypertension >75%
			3-year mortality 14%

CLINICAL PRESENTATION

Patients are asymptomatic in the early stages of CKD, most patients do not come to medical attention until most of their kidney function has been lost. Features of advanced CKD disease include fatigue, anorexia, nausea, morning vomiting, malnutrition, pruritus, bone pain, impotence, amenorrhea, epistaxis, easy bruising, myopathy, muscle twitching and cramps, nail changes, uremic frost on skin surfaces, pleurisy, pericarditis, edema, volume overload, lethargy, confusion, asterixis, peripheral neuropathy, seizures, and coma. Hypertension and proteinuria are the most common features of CKD and are present at all stages of the disease.

Progressive metabolic acidosis develops when renal ammoniagenesis fails and impairs tubular acid excretion. If untreated, metabolic acidosis leads to osteodystrophy (through bone buffering), skeletal muscle breakdown, and diminished albumin synthesis. Gastrointestinal bleeding may occur secondary to platelet dysfunction and diffuse mucosal erosions through the gut. Uremia leads to impaired capillary permeability, fluid accumulation, and

uremic serositis, a syndrome characterized by pericarditis, pleural effusions, and ascites.

Renal osteodystrophy results from secondary hyperparathyroidism (caused by hyperphosphatemia and hypocalcemia, marked parathyroid hypertrophy, and bony resistance to the action of parathyroid hormone) and metabolic acidosis. The principal types of bone disease in CKD are osteitis fibrosis (resulting mainly from secondary hyperparathyroidism) and adynamic bone disease (resulting from oversuppression of parathyroid hormone).

In CKD all organ systems are affected, but the most evident complications include anemia and associated easy fatigability; decreasing appetite with progressive malnutrition, abnormalities in calcium, phosphorus, and mineral-regulating hormones, such as $1,25(OH)_2D_3$ (calcitriol) and parathyroid hormone (PTH); and abnormalities in sodium, potassium, water, and acid-base homeostasis.

The cause of anemia in patients with CKD can be multifactorial with a central component being a relative deficiency of erythropoietin an erythrocyte-stimulating protein that is normally produced by renal parenchymal cells in response to blood partial

pressure of oxygen. Anemia caused by CKD is present in 20 percent of patients with stable coronary disease and 30 to 60 percent of patients with HF. Hence anemia is a common and easily identifiable potential diagnostic and therapeutic target [10,11] .

Hypertension, like anemia, is almost universal in CKD patients and often is the first sign of CKD. Hypertension contributes to the development of cardiovascular disease, the leading cause of morbidity and mortality in CKD patients. Hypertension in CKD patients is mainly the result of an expanded extracellular volume from a salt-rich diet and a decreased capacity for excretion of sodium. Another mechanism for hypertension in CKD patients is activation of the renin-angiotensin-aldosterone (RAA) system and the sympathetic nervous system. Evidence for activation of the RAA system in CKD patients includes circulating levels of renin and aldosterone that are too high for individuals who are hypertensive, suggesting that the vasoconstrictive action of angiotensin II and the salt retention induced by aldosterone contribute to hypertension. Patients with hypertension frequently have serum uric acid values in the upper range of normal or at supranormal levels and this can cause vascular damage,

suggesting that uric acid could play a role in the genesis of hypertension in CKD.

Evaluation

Evaluation of CKD should include measurements of GFR and the degree of albuminuria. Most studies of cardiovascular outcomes have found that a critical cut point for the development of various adverse effects , is an eGFR of 60 ml/min/1.73 m^2, which roughly corresponds to a serum creatinine greater than 1.5 mg/dl in the general population[12, 13] Because Cr is a crude indicator of renal function and often underestimates renal dysfunction in women and the elderly, calculated measures of eGFR or Cr clearance using the Cockcroft-Gault equation or the Modification of Diet in Renal Disease equation are superior methods for the assessment of renal function.

The four-variable Modification of Diet in Renal Disease equation for eGFR is the preferred method because it does not rely on body weight [14] The equation for MDRD is

Estimated GFR (mL/min per 1.73 m^2) = 1.86 x $(P_{Cr})^{-1.154}$ x $(age)^{-0.203}$

Multiply by 0.742 for women and 1.21 for African Americans

Cockcroft-Gault equation

e GFR =(140-Age)× body weight in Kg ÷ (72 × Cr in mg/dl) ,

Multiply by 0.85 for women.

Cr means serum creatinine.

Proteinuria is the most frequent early indicator of kidney damage. While an accurate 24-h urine collection is the "gold standard" for measurement of albuminuria, the measurement of albumin-to-creatinine ratio in a spot first-morning urine sample is often more practical to obtain and correlates well .Persistence in the urine of >17 mg of albumin per gram of creatinine in adult males and 25 mg albumin per gram of creatinine in adult females usually signifies chronic renal damage A recently approved blood test reflecting renal filtration function is the cystatin C test.[15] Cystatin C is a nonglycosylated, low-molecular-mass (13 kDa) protein produced by all nucleated cells. Serum levels of cystatin C are independent of weight and height, muscle mass, age, and sex, making it less variable than Cr.

ASSESSMENT OF PROTEINURIA

	Urine Collection Method	Normal	Microalbuminuria	Albuminuria or Clinical Proteinuria
Total protein	24-hour excretion Spot urine protein/ creatinine ratio	< 300 mg/day < 200 mg/g	NA NA	> 300 mg/day > 200 mg/g
Albumin	24-hour excretion Spot albumin-specific dipstick	< 30 mg/day < 3 mg/dl	30–300 mg/day > 3 mg/dl	> 300 mg/day NA
	Spot urine albumin/ creatinine ratio	< 17 mg/g (men) < 25 mg/g (women)	17–250 mg/g (men) 25–355 mg/g (women)	> 250 mg/g (men) > 355 mg/g (women)

Markers of kidney damage other than proteinuria include abnormalities in the urine sediment and abnormalities on imaging studies. Urine sediment examination or

dipstick for red blood cells and white blood cells should be performed in all patients with CKD. Imaging of the kidneys should be performed in all patients with CKD to evaluate for structural abnormalities, impaired renal blood flow, and urinary obstruction. Imaging should begin with renal ultrasonography but may also include computed tomography or magnetic resonance imaging.

Calcium and Phosphate metabolism in CKD

Normal serum levels of phosphorus and calcium are maintained through the interaction of two hormones: parathyroid hormone (PTH) and 1,25$(OH)_2$D (calcitriol). These hormones act on three primary target organs: bone, kidney, and intestine. The kidneys play a critical role in the regulation of normal serum calcium and phosphorus concentrations, thus derangements are common in patients with chronic kidney disease (CKD). Abnormalities are initially observed in patients with glomerular filtration rate (GFR) levels less than 60 mL/min and are nearly uniform at a GFR less than 30 mL/min.

Chronic kidney disease (CKD) is associated with a number of important disturbances in mineral metabolism,

which include hypocalcemia, hyperphosphatemia, and abnormalities in vitamin D metabolism that result in functional calcitriol deficiency.[16]Elevated plasma levels of parathyroid hormone (PTH), a key calcium-regulating hormone that also affects renal phosphorus excretion, and fibroblast growth factor 23, a recently identified phosphorus-regulating hormone, occur often.[17,18] The major consequences of disordered mineral metabolism in CKD are secondary hyperparathyroidism, metabolic bone disease, and extra skeletal calcification.[19,20]

Studies have demonstrated that the serum phosphorus and the calcium × phosphorus product are associated with poor outcomes in CKD. The association of elevated serum phosphorus and mortality has been confirmed in several studies. Block and colleagues used a large dialysis data base of more than 40,000 patients undergoing hemodialysis in the United States and found an association with increased mortality for phosphorus levels greater than 5.0 mg/dL, with a progressive increase in mortality with increasing levels.[21] In this same study, the relative risk of death correlated directly to serum calcium levels, increasing 47% as the calcium level increased from 9 to 9.5 mg/dL to more than 11 mg/dL..

Epidemiologic studies have revealed the major cause of death in the presence of hyperphosphatemia and hypercalcemia to be cardiovascular events.[22] Studies have demonstrated an association of hyperphosphatemia with increased vascular stiffening, arterial calcification and calciphylaxis and valvular calcification.[23]

VASCULAR CALCIFICATION IN CKD

There is high prevalence of vascular calcification in patients with CKD. Calcium can be deposited into either the medial or intimal layers of the vasculature. Calcium deposition in the medial layer, a common finding in dialysis patients, is associated with stiffening of the vasculature, resulting in significantly adverse cardiovascular outcomes. Intimal calcium deposition is principally associated with atherosclerotic plaques; in patients with normal renal function, such "complex" plaques are more often associated with myocardial infarction and thrombotic events. Compared to those with intimal calcification, patients with medial disease had a longer survival. However, survival was less than that observed in those without calcification

There is evidence for increased arterial calcification in coronary, renal, and iliac arteries from patients on dialysis

compared with nondialysis patients. Braun and associates[24] demonstrated that coronary artery calcification is increased with advancing age in patients on dialysis and that the calcification scores were two to five fold greater in dialysis patients than age-matched individuals with normal kidney function and angiographically proven coronary artery disease. More recent data in patients not yet on dialysis also demonstrates an increased risk of coronary artery calcification, especially in diabetic patients[25]. Nearly 50% to 60% of patients starting hemodialysis have evidence of coronary artery calcification[26]. The only risk factors for coronary artery calcification that are uniform across studies are advancing age and duration of dialysis. Several "modifiable and nonmodifiable" factors that are able to promote vascular calcification are extremely frequent in patients with CKD. Most of the present strategies to decrease vascular calcifications are based in the control of the more prevalent modifiable risk factors. Unfortunately, the extremely important nonmodifiable risk factors, which are highly prevalent, such as older age, time on dialysis, and diabetes, are not under one's control. [27]

Pathophysiology

Vascular calcification is a tightly regulated process that resembles mineralization in bone.[28]Vascular calcification in arteries from ESKD patients is associated with expression of bone matrix proteins and the osteoblast differentiation factor core binding factor alpha-1 (Cbfa1)[29] now called RUNX-2. Runx-2 is thought to be the transcription factor that switches a pluripotent mesenchymal stem cell to the chondrocyte- osteoblast lineage, because animals deficient in RUNX-2 fail to mineralize bone[30]. Non RUNX-2 pathways such as MSX may also be stimulated by bone morphogenic proteins[31] Several nontraditional CKD cardiovascular risk factors can accelerate vascular calcification, including PTH and PTH-related peptide, calcitriol, advanced glycation end products, alterations of lipoproteins, and homocysteine.[28]

Inhibitors of Vascular Calcification

Vascular calcification, although very prevalent in dialysis patients, is not uniform in all. Depending on the series, an average of 17% of dialysis patients have no vascular calcification, and continue to not have calcification on follow up.[27,32]. Younger age is partially responsible for the protection against

calcification and also the presence of naturally occurring inhibitors of calcification. Matrix gla protein (MGP) is a vitamin K-dependent protein expressed in a number of tissues but highly expressed in arteries and bone, where it acts predominantly as a local regulator of vascular calcification. The mechanism by which MGP inhibits extraskeletal calcification appears to be through binding to BMP-2 or modulation of BMP-2 activity, because BMP-2 is known to induce vascular calcification[33]. MGP activity is inhibited by warfarin and in dialysis patients, warfarin is associated with calciphylaxis.[34]. OPG (osteoprotegerin) is another direct inhibitor of vascular calcification but there is conflicting data about this in CKD patients.

Another potential inhibitor of extraskeletal calcification is fetuin-A (α_2-HS glycoprotein). Fetuin-A inhibits the de novo formation and precipitation of the apatite precursor mineral basic calcium phosphate but does not dissolve it once the basic calcium phosphate is formed.[35]. Another naturally occurring inhibitor of mineralization is pyrophosphate. The precise role of these and other inhibitors in the vascular calcification in patients with CKD remains to be determined, but clearly, there are multiple mechanisms to regulate extraskeletal calcification.

Potential Mechanisms of -Vascular Calcification in CKD

There are several different, but not mutually exclusive, mechanisms by which disturbances in mineral and bone metabolism may lead to or accelerate vascular calcification. In the past, a calcium × phosphorus product of 70 mg^2/dl^2 was considered the threshold above which metastatic calcification occurred.Now values more than 56 mg^2 /dl^2 is considered as significant.

Elevations in calcium, phosphorus, and the calcium × phosphorus product can increase extraskeletal calcification by both passive precipitation and by direct effect on vascular smooth muscle cells. Calcium-based phosphate binders also play role in the pathogenesis of vascular calcification. In treat-to-goal study[36] calcification was increased in the calcium-binder treatment arm, whereas there was no increase in the sevelamer(phosphate binder) arm. Another therapy that may increase vascular calcification is vitamin D therapy[37] but not clearly linked to vascular calcification in patients with end stage CKD.

CARDIOVASCULAR DISEASE AND CKD

Patients with kidney failure are at high risk of cardiovascular mortality[38]. They experience a high rate of fatal and nonfatal cardiovascular disease events prior to reaching kidney failure[39,40]. Patients in all stages of CKD are therefore considered in the "highest risk group" for development of cardiovascular disease and CKD is recognized as a cardiovascular risk equivalent[1,42]. CKD is a risk factor for cardiovascular disease and cardiovascular disease may be a risk factor for CKD. Analysis of community-based studies including Atherosclerosis Risk in Communities Study, Cooperative Health Study, Framingham Heart Study, and the Framingham Offspring Study, CKD defined as GFR of 15 to 60 ml/min/1.73 m^2, was an independent predictor of a composite outcome of all-cause mortality as well as fatal and nonfatal cardiovascular disease events[43]. Several studies has established urinary albumin excretion as an independent predictor of cardiovascular outcomes[44] in CKD patients.

Patients with CKD are much more likely to suffer from atherosclerosis and heart failure, resulting in cardiovascular death, than to eventually require renal replacement therapy. This is

likely due in part to accelerated rates of cardiovascular disease among those with CKD. In addition, patients with CKD are more likely to present with atypical symptoms, which may delay diagnosis and adversely affect outcomes. Traditional cardiovascular risk factors, such as hypertension smoking history, diabetes mellitus, dyslipidemia and older age, are highly prevalent in CKD populations[45,46]. Patients with CKD are also more likely to have the metabolic syndrome, which could contribute to the increase in cardiovascular risk[47,48]. Increased arterial stiffness is noted in patients with CKD is also a possible risk factor .Some risk factors are relatively unique to patients with moderate to severe CKD. These include retention of uremic toxins, anemia, increased calcium intake, abnormalities in bone mineral metabolism, and proteinuria.

The overall absolute risk of future adverse cardiovascular events is somewhat lower with CKD patients than that observed in patients with a history of prior heart disease, but without CKD. In general, the risk is approximately 50 percent lower with CKD alone, although the risk increases with increasing renal dysfunction and/or severity of proteinuria. All patients with the same degree of renal dysfunction also do not have the same risk of cardiovascular

disease. Thus, in addition to the evaluation for the presence of CKD, the proper assessment of overall cardiovascular risk requires an adequate assessment for the presence and severity of the other major risk factors for cardiovascular disease

Most common causes of death among patients with CKD[49]

Heart failure	31.2%
Myocardial infarction	15.6%
Sepsis	11.3%
Withdrawal from dialysis	5.2%
Strokes	6.4%
Malignant neoplasm	3.8%
Other	26.5%

ISCHEMIC HEART DISEASE

Ischemic heart disease most commonly results from atherosclerosis of the coronary arteries. The processes that contribute to accelerate atherosclerosis include a dyslipidemia characterized by decreased function of lipoprotein lipase, reduced HDL-C, elevated TG, and elevated LDL-C. Both uremia and dialysis therapy markedly enhance oxidant stress through the production of proinflammatory complement fragments, cytokines, and increased

adhesion molecules in endothelial cells[50]. Endothelial dysfunction begets cardiac and arterial remodeling with resultant cardiovascular events. Potentially important in the inflammatory cascade and ensuing cardiovascular mortality among kidney patients are C-reactive protein (CRP) and asymmetric dimethyl-arginine.

HEART FAILURE

About 40% of people starting dialysis therapy have a history of heart failure symptoms, which is a risk factor for significant morbidity and mortality in this group[51]. For those without heart failure symptoms at the commencement of dialysis, 25% will develop it within 3½ years (7% per year)[52]. Age (risk increased by 30% for every 10 years), female sex, hypertension, diabetes, conditions of atherosclerosis (CAD, cerebrovascular or peripheral vascular disease), pericarditis, and structural cardiac abnormalities (left ventricular hypertrophy, clinical cardiomegaly) were all associated with heart failure. Multiple studies of patients with class II and III HF, in whom a low cardiac output state is not present, have shown decreased survival in a graded fashion related to renal impairment.

VALVULAR HEART DISEASE

Impaired renal function has been linked to valvular calcification and aortic sclerosis. Advanced thickening of the cardiac valves and calcification have been observed in patients with ESRD[53]. Bacterial endocarditis may develop in patients with ESRD who have temporary dialysis access catheters. Most valvular lesions observed in patients with CKD are acquired and develop from dystrophic calcifications of the valvular annulus and leaflets, particularly the aortic and mitral valves. Such calcification is now known to be present far more frequently than previously recognized with a prevalence of up to 55% and 39% for the aortic and mitral valves respectively[54,55]. Once considered benign, aortic valve sclerosis is now also associated with an increased cardiovascular mortality in the general community.

MITRAL ANNULAR CALCIFICATION

Mitral annular calcification is commonly seen in association with aging and in patients with renal failure. Incidence is more common in females. The calcium begins to form in or below the mitral annulus at the junction between the ventricular myocardium

and the posterior mitral leaflet. More severe degrees of calcification will form a pattern resembling the letter *J,* the letter *O,* or a reversed letter *C* . In most instances, mitral annulus calcification has little clinical significance and is a noninflammatory chronic degenerative process. In extreme cases, the mass of calcification can grow posteriorly into the ventricular myocardium to produce heart block. It can also grow anteriorly into the leaflets of the mitral valve to cause mitral regurgitation and stenosis. Rarely, the calcification can erode through the endocardium and cause small systemic emboli. Mitral annulus calcification in the elderly is associated with a doubled risk of stroke, independent of the traditional risk factors.

Two large observational series showed that MAC was present in 8 percent of subjects with a mean age of 57[56] and 48 percent of subjects with a mean age of 81 [57]. MAC is associated with atherosclerosis, thromboembolic events (including stroke) and, in some series, atrioventricular conduction defects [58,59]. Patients with MAC may also have calcification of the aortic annulus, aortic valve, aortic root, sinotubular junction, papillary muscle tips, and systemic calcified atherosclerosis. In an electron beam CT study, MAC was significantly associated with calcific atherosclerosis in the ascending

and thoracic aorta and the carotid arteries, but not the coronary or iliac arteries [58]. Mitral annular calcification is infrequently associated with hemodynamically important mitral insufficiency, mitral stenosis, or endocarditis [60,61].

MAC, like calcific aortic valve disease, is associated with standard cardiovascular risk factors. However, Kizer et al[62] recently showed that the presence of MAC but not of aortic valve sclerosis was a strong risk factor for incident stroke in a cohort of American Indians without clinical cardiovascular disease after extensive adjustment for other predictors.

A lesser known variant of MAC, is caseous calcification of the mitral annulus. It is described as "a round mass with a central echolucent area composed of a puttylike admixture of fatty acids, cholesterol, and calcium"[63] . This variant of MAC carries a benign prognosis; however, it is important that it not be mistaken for a cardiac tumor [64,65].

The echocardiographic appearance of MAC is characteristic and easily recognized. In the long axis view, it appears as a bright reflection most commonly in the posterior atrioventricular groove, which shadows objects behind it. As the severity of

calcification increases, the mass appears to grow into the myocardium of the left ventricular base and its inflow tract. Unless care is exercised, the process may be mistaken for posterior leaflet calcification because the mass and its ultrasonic side lobe artifacts obscure that relatively short structure. In the short axis view, careful angulation will reveal its typical C-shaped morphology and its location between the papillary muscles, from four to eight o'clock.

Mitral annular calcification in CKD

Mitral annular calcification (MAC) occurs in 10 to 50 percent of patients with end-stage renal disease [66,67].It is associated with an elevated calcium-phosphorus product, vascular calcification, hypercalcemia, and hyperphosphatemia. MAC occurs earlier in patients with chronic renal failure than those without renal dysfunction. In one study, MAC was more common in younger (less than 60 years of age) than older dialysis patients [67]. Since older dialysis patients are commonly dialyzed for fewer years because of a marked increase in mortality, MAC appears to occur more frequently in those dialyzed for a longer period of time.

AIMS AND OBJECTIVE

1 To study the prevalence of mitral annular calcification in chronic kidney disease patients compared to people with normal kidney function

2. To find out various parameters that shows significant association with mitral annular calcification in chronic kidney disease patients

MATERIALS AND METHODS

Setting	: Department of Medicine , Govt Rajaji hospital Madurai
Design	: case control study
Period of study	: six months study
Ethical approval	: Obtained from ethical committee approval headed by Dean, Govt. Rajaji hospital
Consent	: Informed consent obtained from all patients
Study population	: Patients attending outpatient department or wards with chronic kidney disease
Control group	:Persons comparable in age and sex with study group without kidney disease
Collaborating Departments	: Department of Cardiology Department of Nephrology
Financial support	: Nil
Conflict of interest	: Nil

SELECTION AND DETAILS OF STUDY SUBJECTS

In the study group ,102 chronic kidney disease patients who attended the outpatient department or wards of Government Rajaji Hospital Madurai, fulfilling the inclusion criteria were selected randomly. Informed consent was obtained from all.

Inclusion criteria

eGFR< 60 ml/min/1.73m^2.

Documented elevated renal parameters for > 3 months.

… Ultrasonography suggestive of chronic kidney disease.

Exclusion criteria

eGFR > 60 ml /min/1.73m^2.

Patients who underwent renal transplant.

Patients with valvular heart disease of other causes.

Duration of disease less than 3 months.

Patients with obstructive uropathy.

Patients not given consent.

The control group of 100 persons comparable to study group in age and sex distribution and not having kidney disease ,were selected and evaluated.

Data collection

Profoma containing details regarding age, sex, history of diabetes mellitus, hypertension, coronary artery disease ,cerebrovascular disease ,vital data and blood investigation and imaging studies were filled up for all participants.

Participants who were receiving oral hypoglycemic drugs or insulin and those who had fasting glucose level >126mg/dl or postprandial glucose level > 200mg/dl were defined as diabetic.

Hypertension was defined as participants having

systolic blood pressure > 140 mm of Hg or

diastolic bloodpressure > 90 mm of Hg or

those receiving medication for hypertension

An average of at least two readings of blood pressure were taken in all participants.

Kidney function assessment

kidney function assessment was estimated by GFR using **Cockcroft-Gault** equation

e GFR =(140-Age) × body weight in Kg ÷ (72 × Cr in mg/dl).

, Multiply by 0.85 for women.

Cr means serum creatinine.

In this study definition of CKD was based on the National Kidney Foundation Kidney Disease Outcomes Quality Initiative working group definition of CKD as a GFR < 60 ml/min per 1.73 m^2 .

Echocardiographic Evaluation

All the participants in study were subjected to echocardiographic evaluation (using Philips IE 33). Mitral annular calcification was considered present when an echo-dense band was visualized in the region of the mitral annulus that was >0.3 cm thick on the M-mode or when the two -dimensional study demonstrated calcification of more than one third of the circumference of the

annulus in the parasternal short-axis view .For all determinations of valvular calcification, interpreters confirmed visualization in more than one view.

ULTRASONOGRAPHY

Ultrasonographic evaluation of all participants in the study were done to assess the presence of chronic kidney disease based on following parameters (1) increase in cortical eccogenicity (2) loss of corticomedullary differentiation (3) and contracted kidney .

BIOCHEMICAL EVALUATION

All the participants were evaluated for haemoglobin ,blood urea, serum creatinine , calcium, phosphorus, and potassium based on standard tests available in our hospital. Presence of albuminuria was also done in all participants.

RESULTS AND OBSERVATIONS

CHARACTERISTICS OF CASES AND CONTROL GROUPS

SEX DISTRIBUTION

Table. 1 sex distribution

	Study Group			Control Group		
	Female	Male	Total	Female	Male	Total
No	39	63	102	35	65	100
%	38.2	61.8	100.0	35.0	65.0	100.0

Chi Square test: p Value=0.663

Among 102 patients included in study , 63 (61.8%) were males and 39 (38.2 %) were females .In control group 65 % were males and 35 % were females(p value = 0.663) and the two groups were comparable

AGE DISTRIBUTION

Both groups had similar age distribution and were comparable (P value 0.9 - Not significant)

Table.2 Age distribution

			Group		Total
			Study Group	Control Group	
Age group	<40 YRS	No	23	24	47
		%	22.5%	24.0%	23.3%
	40-60 YRS	No	56	56	112
		%	54.9%	56.0%	55.4%
	>60 YRS	No	23	20	43
		%	22.5%	20.0%	21.3%
Total		No	102	100	202
		%	100.0%	100.0%	100.0%

Chi Square test: p Value=0.9

Table.3 Diabetic status

				Total
		Study Group	Control Group	
Non diabetic	No	76	79	155
	%	74.5%	79.0%	76.7%
Diabetic	No	26	21	47
	%	25.5%	21.0%	23.3%
	No	102	100	202
	%	100.0%	100.0%	100.0%

Chi Square test: p Value=0.507

In study group 26 (25.5%) were diabetic and in control group 21 (21%) were diabetic and there was no significant difference.

Table. 4

Hypertension

				Total
		Study Group	Control Group	
Non-Hypertensive	No	18	80	98
	%	17.6%	80.0%	48.5%
Hypertensive	No	84	20	104
	%	82.4%	20.0%	51.5%
	Total No	102	100	202

Chi Square test: p Value < 0.001***

In the study group 84 (82.4%) were hypertensive compared 20% in control group. P value < 0.001 shows that hypertension was significantly high in chronic kidney disease patients.

Table.5

Coronary Artery Disease

		Study Group	Control Group	Total
No CAD	No	82	81	163
	%	80.4%	81.0%	80.7%
CAD present	No	20	19	39
	%	19.6%	19.0%	19.3%
	Total	102	100	202

Chi Square test: p Value=0.913

Coronary artery disease was present in 20 (19.6%) among study group . In control group 19 (19 %) had CAD. (P value 0.93 not significant)

Albuminuria

Albuminuria was present in 74 (72.5%) in study group and in control group only 8% had albuminuria.

Table. 6

Albuminuria

				Total
		Study Group	Control Group	
No Albuminuria	No	28	92	120
	%	27.5%	92.0%	59.4%
Albuminuria	No	74	8	82
	%	72.5%	8.0%	40.6%
	Total	102	100	202

Chi Square test: p Value < 0.001***

OTHER PARAMETERS

In this study mean age is 51.35 and 49. 3 years in study and control groups respectively. Hemoglobin and calcium levels were significantly (p value < 0.001) low in study group when compared to control group. Mean hemoglobin and calcium levels were 8.3 gm % and 8.6 mg/ dl in study group and 11.7 gm % and 9.42 mg /dl in control group respectively.

Table. 7 Characteristics of two groups

Parameters	Group	Mean	Std. Deviation	Independent T-test(p Value)
Age (yrs)	Study Gp	51.35	11.750	0.326
	Control Gp	49.73	11.688	
Hemoglobin (gm %)	Study Gp	8.380	1.8093	0.000***
	Control Gp	11.797	1.7222	
Blood Sugar (mg /dl)	Study Gp	125.31	46.482	0.000***
	Control Gp	101.64	17.774	
Sr Calcium (mg/dl)	Study Gp	8.60	.796	0.000***
	Control Gp	9.42	.575	
Sr Potassium (Mmol/L)	Study Gp	4.852	.6161	0.000***
	Control Gp	4.218	.4024	
Weight(kgs)	Study Gp	57.02	8.151	0.000***
	Control Gp	61.94	6.279	

Dialysis in study group

Among 102 patients in study group 37 (36.3 %) were on hemodialysis and 65 (63.7 %) were not undergone dialysis.

Table. 8

Dialysis status

		No.	%
Study Group	Not on Dialysis	65	63.7
	Dialysis done	37	36.3
	Total	102	100.0

Table. 9

MITRAL ANNULAR CALCIFICATION

	ECHO cardiogram			
	MAC absent		MAC present	
	No.	%	No.	%
Study Group	92	90.2%	10	9.8%
Control Group	99	99.0%	1	1.0%

Chi Square test: p Value=0.010**

In the study group 10 (9.8 %) among 102 patients had mitral annular calcification .In the control group only 1 (1%) had mitral annular calcification .p value is significant.

Table. 10

MAC in various eGFR groups

			ECHO		Total
			MAC present	MAC absent	
CKD Stage	<15 ml/min	No	46	7	53
		%	50.0%	70.0%	52.0%
	15-30 ml/min	No	30	3	33
		%	32.6%	30.0%	32.4%
	30-60 ml/min	No	16	0	16
		%	17.4%	0%	15.7%
Total		No	92	10	102
		%	100.0%	100.0%	100.0%

Chi Square test: p Value=0.293

Among 10 patients who had MAC in study group,7 (70 %) were in the group with eGFR < 15 ml/min and 3 (30 %) were in group with eGFR 15 to 30 ml/min.P value is 0.29 and not significant. Calcification was not present in the group with eGFR 30 to 60ml/min.

Table. 11

MAC age distribution

			ECHO cardiogram		Total
			MAC absent	MAC present	
Age group	<40 YRS	No	23	0	23
		%	25.0%	0%	22.5%
	40-60 YRS	No	50	6	56
		%	54.3%	60.0%	54.9%
	>60 YRS	No	19	4	23
		%	20.7%	40.0%	22.5%
Total		No	92	10	102
		%	100.0%	100.0%	100.0%

Chi Square test: p Value 0.048

Among 10 calcification observed, 60 % were in age group 40 to 60 years and 40 % in above 60 years.

In the control group only 1 (1%) calcification observed was in age group above 60 years.

Table .12

Association of MAC with various parameters

		No	Mean	Std. Deviation	T test (p value)
Age (yrs)	MAC -	92	50.67	11.941	.077
	MAC +	10	57.60	7.706	
Creatinine (mg/dl)	MAC -	92	5.704	3.7193	.449
	MAC +	10	5.180	1.7637	
Hemoglobin (gm %)	MAC -	92	8.336	1.8367	.454
	MAC +	10	8.790	1.5560	
Sr Calcium (mg / dl)	MAC -	92	8.54	.771	.018**
	MAC +	10	9.16	.842	
Potassium (mmol/L)	MAC -	92	4.839	.6228	0.526
	MAC +	10	4.970	.5658	
Phosphorous (mg/ dl)	MAC -	92	4.6489	.46303	0.000***
	MAC +	10	5.5200	.27809	
Ca X Po4 (mg^2/dl^2)	MAC -	92	39.5653	4.53871	0.000***
	MAC +	10	50.4560	4.34803	

P value is significant for association with serum calcium , phosphorus and calcium phosphorus product .

Table.13

MAC and diabetes

				Total
		MAC -	MAC +	
Non-diabetic	No	71	5	76
	%	77.2%	50.0%	74.5%
Diabetic	No	21	5	26
	%	22.8%	50.0%	25.5%
Total	No	92	10	102
	%	100.0%	100.0%	100.0%

Chi Square test: p Value=0.118

Among 10 patients having MAC 50 % were diabetic. p value is not significant.

MAC sex distribution

Among 10 calcification in CKD patients, 5 were in males and 5 were in females showing no significant sex predilection.

Table.14

MAC and dialysis

		ECHO cardiogram	
		MAC-	MAC+
Not Dialysed	N	59	6
	%	64.1%	60.0%
	% of Total	57.8%	5.9%
Dialysed	N	33	4
	%	35.9%	40.0%
	% of Total	32.4%	3.9%
Total	N	92	10
	%	100.0%	100.0%
	% of Total	90.2%	9.8%

Chi Square test: p Value=0.796

In the study 3.9% of dialysed patients and 5.9 % of non dialysed patients had mitral annular calcification. P value is 0.79 and not significant.

Table.15

CAD and MAC

		ECHO cardiogram	
		MAC absent	MAC present
CAD Absent	N	79	3
	%	85.9%	30.0%
CAD present	N	13	7
	%	14.1%	70.0%
Total	N	92	10
	%	100.0%	100.0%

Chi square Test: p Value< 0.001****

In CKD patients with MAC 70 % had coronary artery disease compared to 14.1 % in patient not having MAC .

DISCUSSION

In India the approximate prevalence of CKD is 800 per million population (pmp) and the incidence of end-stage renal disease (ESRD) is 150-200 pmp[68].MAC occurs earlier in patients with chronic kidney disease than those without renal dysfunction and is associated with atherosclerosis and thromboembolic events (including stroke).

In this study , the main aim was to find out the prevalence of mitral annular calcification in patients with chronic kidney disease as compared to those with out chronic kidney disease. Beyond that association of mitral annular calcification with various parameters like age , sex , diabetic status ,serum calcium , serum phosphorus , calcium x phosphorus product , estimated GFR and dialysis were also observed .

Among 102 patients who were allotted to study group 63 (61.8 %) were males and 39 (38. 2 %) were females. In the control group 65 % were males and 35 % were females.

In the study group 26 % were diabetic while 21 % in control group. Prevalence of hypertension and coronary artery disease were 82.4 % and 19.6 % in study group and 20 % and

19 % in control group respectively. Albuminuria was present in 72.5 % of patients with CKD.

The two groups were comparable in age and sex distribution .CKD group had significant anemia (mean Hb 8.3 gm%) compared to control group(mean Hb 11.7 gm %) P value < 0. 001. Calcium level was also significantly low in CKD group (mean 8.6 mg/dl) than control group (mean 9.42). Potassium level was high in CKD patients (4.85 mmol/L) compared to non CKD group(4.2 mmol/L) p value< 0.001. Anemia , hypocalcemia and hyperkalemia are well documented features of chronic kidney disease .

Mitral annular calcification was present in 9.8 % of patients with chronic kidney disease while only 1% had calcification in non CKD group; which shows that there is significantly high prevalence of MAC in CKD patients (p valve 0.010) . In Framingham heart study[69] on "Association of kidney function with valvular and annular calcification", prevalence of mitral annular calcification were 12 % and 3 % in CKD and non CKD groups respectively. In "Atherosclerotic Risk in Communities study", the overall prevalence of MAC was 4.6% for women and 5.6% for men.[70] In participants aged

70 years and older, the prevalence of MAC was 10% in women and 15.2% in men.[70]

In this study , CKD patients with MAC, 70% had eGFR < 15 ml / min/1.73m^2 and 30 % had between 15 to 30 ml/min/1.73m^2. There is no significant difference in MAC among various eGFR groups(p value 0.293). In a Study by Folkert W. Asselbergs & Dariush Mozaffarian, the prevalence of MAC were significantly high in individuals with eGFR < 45 mL/ min/1.73 m^2 (P < 0.01).

This study showed in CKD patients MAC was present in 60% and 40% in age group 40 to 60 years and obove 60 years respectively. No calcification was found in age group below 40 (p value 0.048). In non CKD group calcification was present only in above 60 age group .Usually MAC can be seen in elderly individuals. In CKD patients it is more prevalent and also occur in younger age group.

This study shows significant association between mitrall annular calcification in CKD patients with high serum levels of calcium, phosphorus and calcium x phosphorus product. Mean serum

calcium level in CKD patients with MAC (9.16mg/dl) was significantly high compared to patients without MAC (8.54mg/dl) P value 0.018. Serum phosphorus in MAC group (5.5 mg/dl) also was significantly higher than CKD patients without MAC(4.6mg/dl) $p < 0.001$. Mean Calcium x phosphorus product in CKD patients with MAC ($50.4 mg^2/dl^2$) was significantly higher than CKD patients without MAC ($39.5 mg^2/dl^2$) P value < 0.001.

In study done by Maher ER, Young G[71] MAC showed association with increased calcium X phosphorus product and long-term hemodialysis in CKD patients. Study done by Ribeiro S, Ramos et al [72]showed positive correlation between age and Ca x P product with cardiac valvular calcification. This study states that in dialysis patients age and calcium phosphorus product as the most predictive parameters for valvular calcification

This study does not show any significant association between mitral calcification and diabetic status (P value 0.118). Association between MAC and gender also was insignificant .

This study does not show significant increase in mitral calcification in chronic kidney disease patient who were on

dialysis .Various studies have shown that presence of MAC increases with duration of dialysis. Disparity may be due to that, many of the dialysis group patients in this study, were not on regular dialysis and duration of dialysis was not taken into account. In Study by Yusuf and Selcoki Faruk, longer duration of dialysis was associated with mitral valve calcification.

This study showed significantly high association of coronary artery disease in CKD patients with mitral calcification than those with out calcification. 70 % of those with MAC had CAD compared to 14.1% in CKD patients without MAC ($P < 0.001$).The study by Fox CS, Vasan RS et al [73] showed independent association of MAC with incident CAD and CAD death and suggest cardiac calcification as a marker of increased CAD risk. The association between MAC, and increased cardiovascular risk may also be due to the burden of shared risk factors, including age, hypertension, hyperlipidemia, diabetes, and obesity.

CONCLUSION

1 The prevalence of mitral annular calcification in chronic kidney disease patients was 9.8% compared to 1% in people with normal kidney function.

2 Mitral annular calcification showed significant association with high serum calcium , phosphorus and calcium x phosphorus product in CKD patients.

3 No significant association was noticed between diabetes , dialysis status and gender with mitral annular calcification.

4.Mitral annular calcification occurs at an earlier age in CKD patients.

5 Coronary artery disease was significantly high in patients with mitral annular calcification.

SUMMARY

A case control study was conducted on prevalence of MAC in chronic kidney disease patients compared to subjects with normal kidney function. After obtaining ethical committee clearance , 102 CKD patients and 100 non CKD subjects comparable in age and sex distribution were selected randomly. After recording clinical data, blood investigations and ultrasonographic study, echocardiogram was done in all to look for MAC

Results on analysis showed significantly high MAC in CKD patients. Among 102 CKD patients 10(9.8%) had MAC while only one(1%) had MAC in non CKD group. Among 10 who had MAC in CKD group, 6 (60%) were in 40 to 60 age group and 4 (40%) were in above 60 age group. In non CKD group MAC was present only in an elderly female. In CKD patients MAC occurs even in younger age group. Significant association of high levels of calcium, phosphorus and calcium x phosphorus product with MAC was also noticed in the study. Increased MAC in CKD patients may be due to altered calcium and phosphorus metabolism in them. CAD was significantly high in those with MAC which may be due to the burden of shared risk factors for atherosclerosis in both groups.

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PROFOMA

MITRAL ANNULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE

NAME AGE SEX

ADDRESS

CLINICAL DETAILS

HISTORY

DIABETES HYPERTENSION CAD CVA

OTHERS

EXAMINATION

PR BP WEIGHT

INVESTIGATIONS

Hb CALCIUM

BLOOD SUGAR PHOSPHORUS

UREA POTASSIUM

CREATININE Ca X P

e GFR URINE Alb

USG ABDOMEN

ECHO FINDING

GLOSSARY

CKD - Chronic kidney disease

ESRD - End Stage Renal Disease

MAC - Mitral Annular Calcification

GFR - Glomerular Filtration Rate

RAA - Renin Angiotensin Aldosterone

eGFR - estimated Glomerular Filtration Rate

MDRD - Modification of Diet in Renal Disease

Cr - Creatinine

PTH - Parathormone

Cbfa 1 - Core binding Factor Alpha – 1

BMP - Bone Morphogenic Protein

MGP - Matrix Gla Protein

OPG - Osteoprotegerin

AGE DISTRIBUTION OF CKD AND NON CKD GROUPS

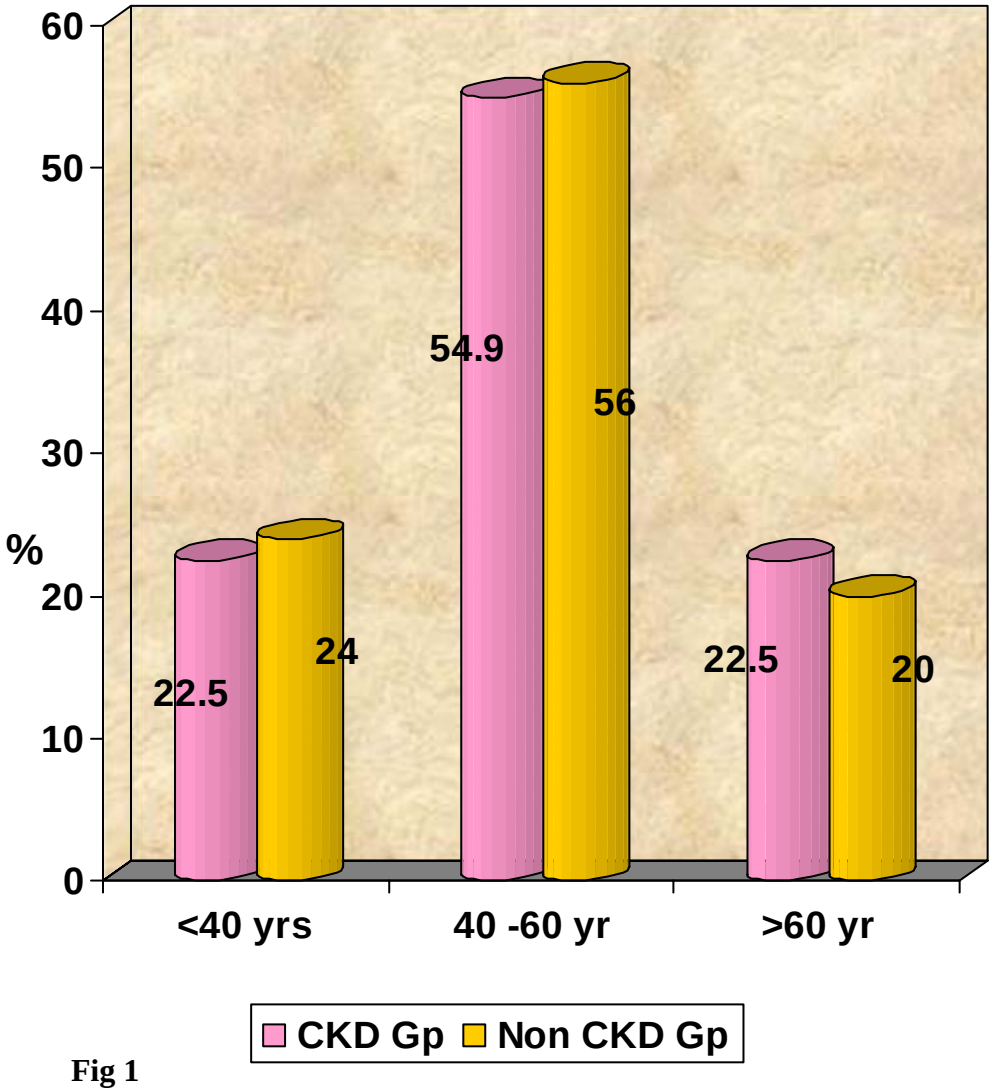


Fig 1

MAC in CKD AND Non CKD Patients

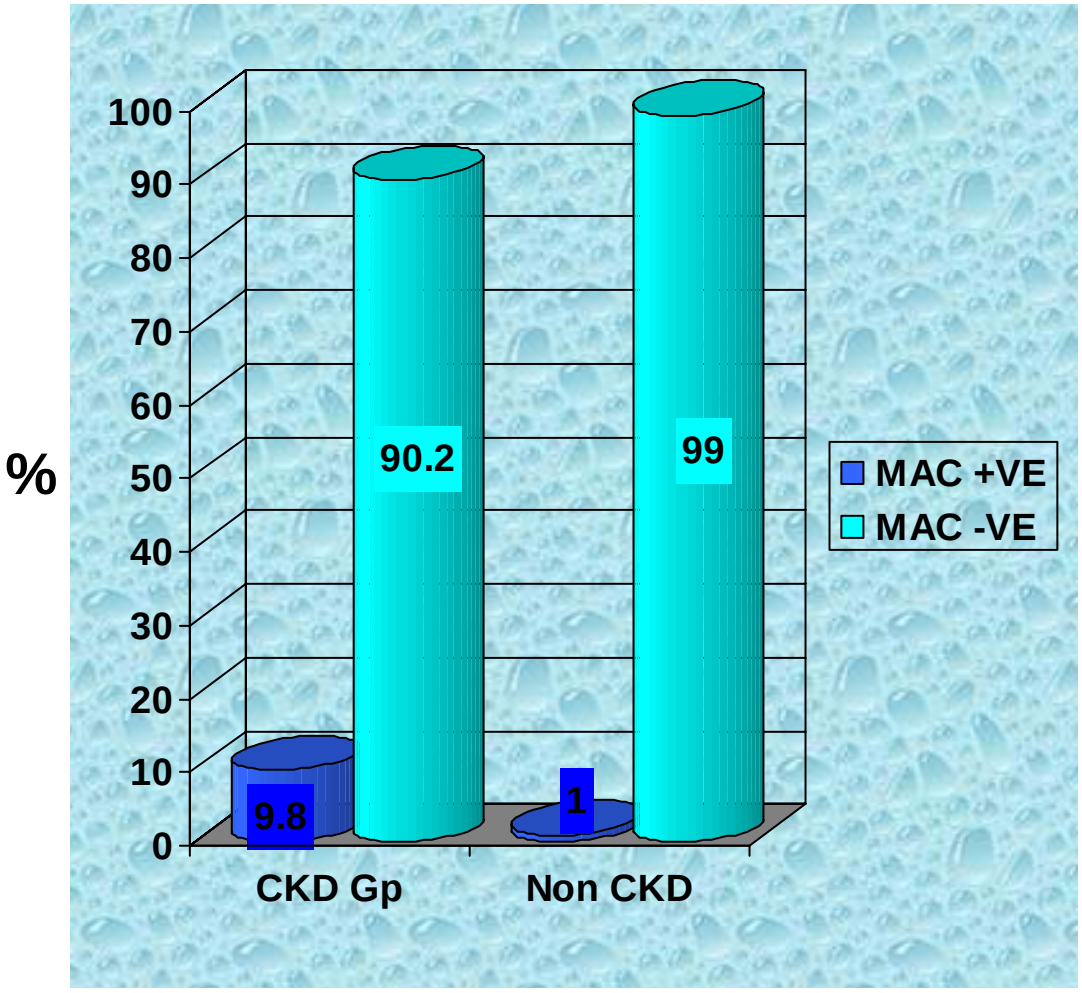
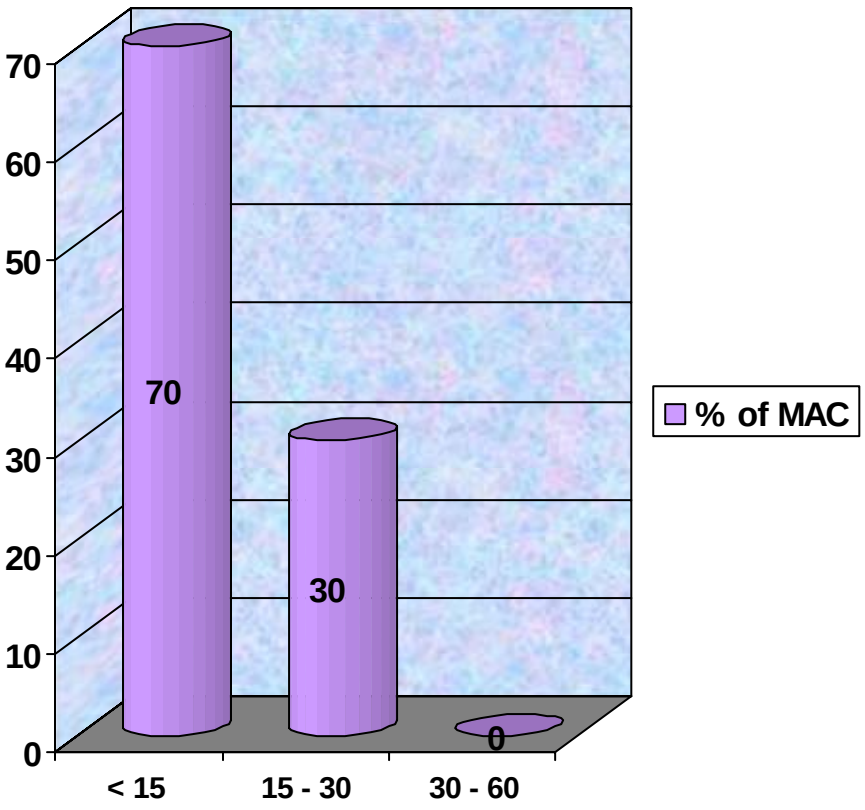


Fig 2

GROUPS

DISTRIBUTION OF MAC

IN VARIOUS eGFR GROUPS IN CKD PATIENTS



eGFR in ml/min/1.73m^2

Fig 3

DISTRIBUTION OF MAC

IN VARIOUS AGE GROUPS IN CKD PATIENTS

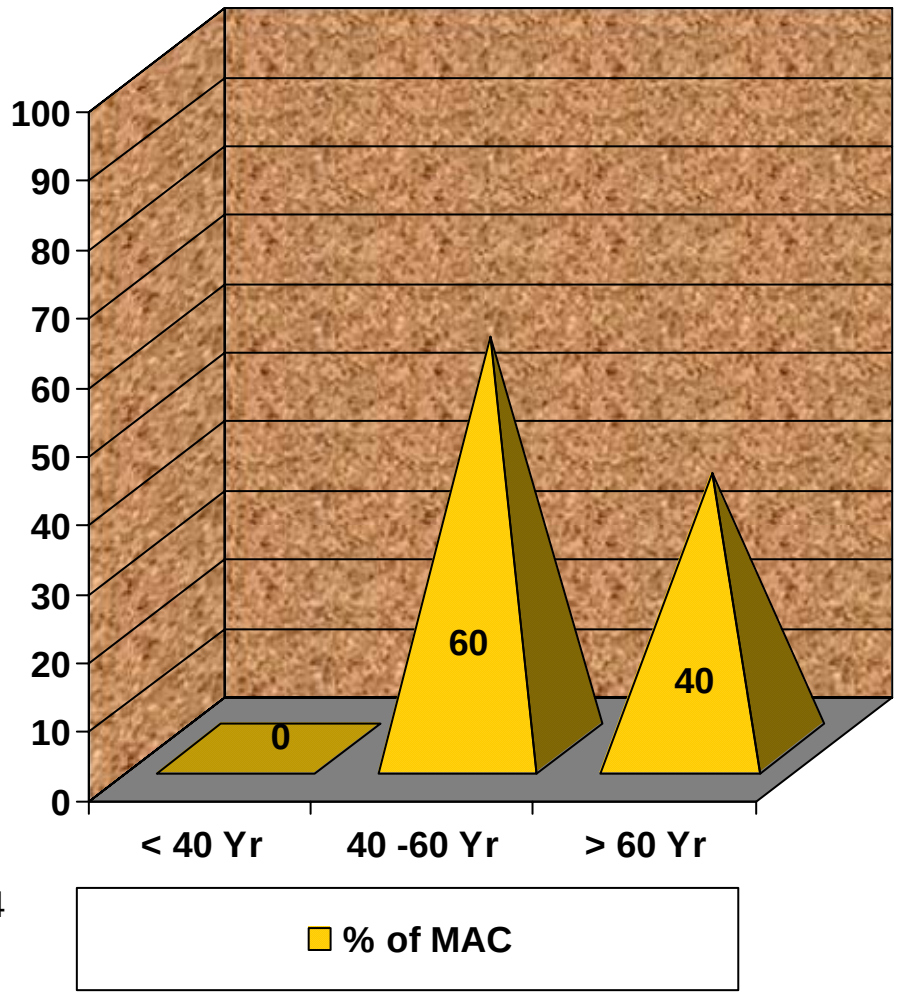


Fig. 4

CAD in CKD patients with and without MAC

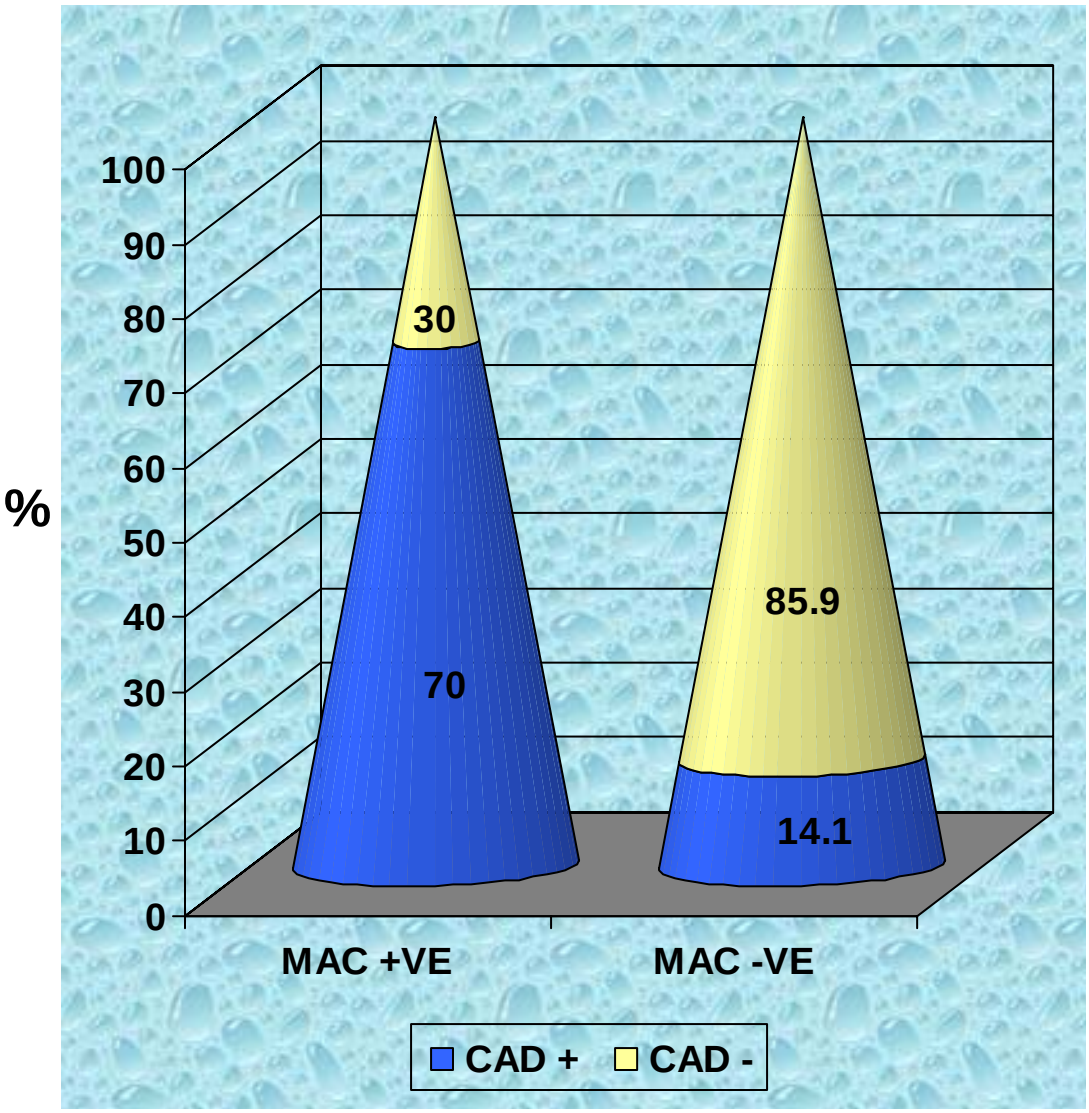
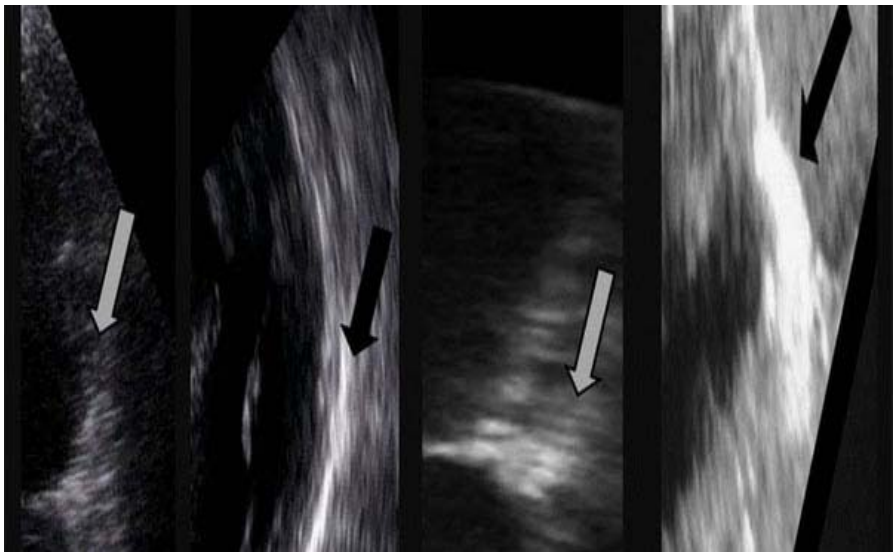
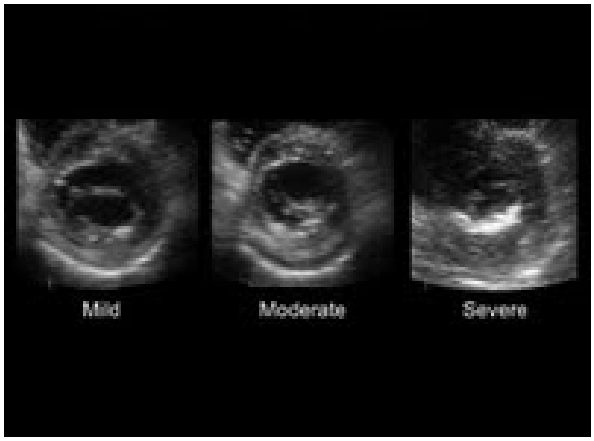


Fig 5

ECHO-NORMAL AND CALCIFIED MITRAL ANNULUS





ETHICAL COMMITTEE APPROVAL

TOPIC :MITRAL ANULAR CALCIFICATION IN CHRONIC KIDNEY DISEASE

ORDER No : K.Dis.No.14931/E4/3/2009

DONE BY : Dr BINJO J VAZHAPPILLY

PLACE : GOVERNMENT RAJAJI HOSPITAL, MADURAI

NO	AGE	SEX	DM	HTN	CAD	CVA	Hb	RBS	UREA	Cr	Ca	K	P	Ca x P	Ur. Alb	Weight	eGFR	Echo	USG	DIALYSIS
1	75	F	-	+	+	-	6.1	138	94	4.3	8	4.5	5	40	+	52	9.56	N	CKD	ND
2	42	M	-	+	-		9	86	46	1.4	9	4.2	4	36	-	60	58	N	CKD	ND
3	44	M	-	+	-	-	6.4	125	179	16.5	7.8	6	5.2	40.56	+	62	5	N	CKD	D
4	33	M	-	-	-	-	5.9	120	40	1.8	8.4	3.2	3.9	32.76	-	64	52.8	N	CKD	ND
5	20	M	-	+	-	-	10	80	109	9.6	7.5	4.4	4	30	+	58	10	N	CKD	D
6	31	M	-	+	-	-	5.7	74	74	7.2	8	6	4.5	36	+	52	10.9	N	CKD	ND
7	63	M	-	+	+	-	9.3	184	40	6	9.9	4.8	5.8	57.4	+	48	8.5	C	CKD	D
8	28	F	-	+	-	-	4.3	100	30	8.5	9.1	5.2	4.4	40.04	+	55	16	N	CKD	ND
9	61	F	-	+	+	-	5	240	150	9	8.1	6.4	5	40.5	+	61	7.4	N	CKD	ND
10	33	F	-	+	-	-	7.1	120	130	7.8	8.8	6	5.1	44.88	+	48	7.7	N	CKD	D
11	50	M	-	+	-	-	7.3	170	60	7	8.6	4.9	4.5	38.7	+	62	11	N	CKD	ND
12	51	F	-	+	-	-	5.6	90	70	6.5	9	5.3	4.2	37.8	+	70	13.3	N	CKD	D
13	61	M	+	+	+	-	10	99	70	7.4	10	5.4	5	50	+	65	9.6	C	CKD	ND
14	30	M	+	+	-	-	10	120	100	14	9.2	5.5	5	46	+	60	6.5	N	CKD	ND
15	55	F	-	+	-	-	11	90	40	1.8	8.7	5	4.1	35.67	+	50	27.8	N	CKD	ND
16	45	F	-	+	-	-	8	110	113	11.1	7.9	4.8	4.6	36.3	+	74	8.79	N	CKD	ND
17	54	M	-	+	-	-	12	120	30	4.2	8.2	4.1	4	32.8	+	66	17	N	CKD	ND
18	40	M	-	+	-	-	7	71	83	9	8.8	5.6	5	44	+	57	8.8	N	CKD	D
19	55	F	+	+	-	-	6.4	142	42	4.2	8	5.7	4.3	34.4	+	60	16.8	N	CKD	ND
20	29	F	-	+	-	-	8.5	125	100	7.7	7.5	4.1	4.6	34.5	+	64	12.8	N	CKD	ND
21	45	M	-	+	+	-	10	300	79	6	9.5	4.6	5.4	51.3	+	85	18.6	C	CKD	D
22	64	M	-	-	+	-	9.4	140	60	2.7	9.2	5	4.8	44.16	+	60	23.4	N	CKD	ND
23	59	M	-	+	-	-	9	110	110	9	9	3.5	5	45	+	55	6.9	N	CKD	ND
24	30	M	-	+	-	-	6	120	140	15	8.6	4.2	5.1	43.86	+	60	6.1	N	CKD	D
25	53	M	-	+	-	-	7	200	79	3.8	9	5	4.5	40.5	+	58	18.44	N	CKD	ND
26	49	M	-	+	-	-	8.4	64	61	7.4	8.7	5.2	4	34.8	+	68	11.6	N	CKD	ND
27	59	M	+	+	-	+	8	169	64	8	8.5	5.6	4.8	40.8	+	48	6.75	N	CKD	ND
28	48	F	+	+	+	-	7.8	90	40	4.3	8.8	4.2	5.3	46.64	+	50	12.6	C	CKD	D
29	68	F	-	+	-	-	7	130	89	5	8.5	5.3	4.2	35.7	+	54	9.1	N	CKD	ND
30	58	M	-	+	-	+	5.4	80	170	17	7	4.8	4.1	28.7	+	60	4	N	CKD	D
31	45	M	-	-	-	-	6	90	120	10	7.4	5.4	5.2	38.4	+	50	6.5	N	CKD	ND
32	45	F	-	+	-	-	11	110	38	2	8.3	4	4.6	38.18	-	54	30.2	N	CKD	ND
33	54	F	+	+			7.7	160	66	10	8	5.4	5	40	+	60	7.1	N	CKD	D
34	48	M	-	-	-	-	8.7	90	80	11	8.2	5.4	4.8	39.3	+	74	8.5	N	CKD	D
35	54	M	+	+	-	+	7	104	74	8	9.5	4.8	4.6	43.7	+	60	8.9	N	CKD	ND
36	65	F	-	+	-	-	9	110	140	7	7.2	5.5	4.5	32.4	+	58	8.6	N	CKD	D
37	64	M	-	+	-	-	6	92	64	6	8.5	5	4.3	36.55	-	60	10.5	N	CKD	ND
38	57	F	+	+	-	-	7.5	98	80	4.2	7.4	5.2	6	44.4	+	45	12.3	C	CKD	ND
39	28	F	-	-	-	-	5	90	30	4.5	8.1	5	4.6	37.2	-	56	16.45	N	CKD	ND
40	64	M	-	+	+	-	7.2	200	60	4	7.8	5.2	4	31.2	-	50	15.8	N	CKD	ND
41	65	F	+	+	-	-	6	133	120	8	6.1	5	5.3	32.33	+	55	6.08	N	CKD	D
42	45	F	+	+	-	-	8	110	90	8.6	7.5	4.5	5	37.5	+	68	10.4	N	CKD	ND
43	60	F	-	-	-	-	10	100	116	10	7	4	5.1	35.7	+	60	5.66	N	CKD	ND
44	63	M	-	+	-	-	10	100	200	9.8	7.5	3.5	5.5	41.25	+	54	5.8	N	CKD	D
45	27	M	-	+	-	-	9	95	180	18	7	6	5	35	+	60	5.2	N	CKD	ND
46	47	M	+	-	-	+	8	260	78	2.3	8.5	5	4.8	40.8	-	55	30.88	N	CKD	ND
47	59	M	-	+	-	-	9	220	100	4	8	4.8	4.5	36	-	68	19.1	N	CKD	D
48	60	F	+	-	-	-	8	170	80	3.4	8.5	4	4.2	35.7	+	70	19.44	N	CKD	ND
49	52	F	+	+	+	-	8.6	90	67	2.7	9	4.2	4.8	43.2	-	65	25.1	N	CKD	ND
50	52	M	-	+	-	-	8	110	80	4	7.8	5	4.8	37.44	+	70	21.3	N	CKD	D

NO	AGE	SEX	DM	HTN	CAD	CVA	Hb%	RBS	Urea	Cr	Ca	K	P	Ca xP	Ur. Alb	WEIGHT	eGFR	ECHO	USG	DIALYSIS
51	50	F	-	+	-	-	7.5	120	100	9.3	7	4.6	5	35	+	55	7.39	N	CKD	ND
52	56	M	+	+	-	-	8	180	130	9	7.1	4.8	4.8	34.08	+	80	10.3	N	CKD	D
53	47	M	-	-	-	-	10	110	74	4	9	5	4.9	44.1	-	70	22.6	N	CKD	ND
54	56	M	-	+	-	-	10	76	60	2	9.4	5	5	47	-	50	30	N	CKD	ND
55	40	M	-	+	-	-	9	90	50	3.9	8.6	4.8	5.1	43.8	+	45	16	N	CKD	D
56	52	M	-	-	-	-	8	104	90	2	8.5	4.5	4.4	37.4	+	47	28.7	N	CKD	ND
57	60	F	+	+	+	-	6.2	210	140	7	9	5.5	5.4	48.6	+	55	7.8	C	CKD	ND
58	40	M	-	-	-	-	7	120	60	1.9	9.5	4	4	38	-	60	43.8	N	CKD	D
59	62	M	+	+	-	-	9.2	190	90	5	9.3	5.4	4.1	38.1	+	65	14	N	CKD	ND
60	71	M	-	+	-	-	10	64	100	2.4	8	4.2	4.2	33.6	+	52	20.7	N	CKD	ND
61	50	F		+	-	-	8.6	96	110	3	9.1	4.8	4.7	42.77	-	54	19.1	N	CKD	D
62	50	M	-	-	+	-	7	100	104	5.1	8.8	5.2	4.8	42.24	-	50	12.25	N	CKD	ND
63	42	M		+	-	-	10	110	120	6	8.4	4.8	5	42	+	65	13	N	CKD	ND
64	50	M	-	+	-	-	11.2	86	60	1.8	9.8	4	4.2	41.1	-	55	38	N	CKD	D
65	60	F	-	-	-	-	6.3	80	80	2.7	9.5	5.1	4	38	+	50	17.4	N	CKD	ND
66	43	F	+	+	-	-	9	280	110	4	9	4.5	5	45	+	42	14.1	N	CKD	ND
67	38	M	-	-	-	-	8	90	78	2.1	8.8	4.6	4	35.2	-	62	41.8	N	CKD	D
68	60	M	-	+	+	-	11	160	180	7.1	8.7	5.8	5.6	48.72	+	50	7.2	C	CKD	D
69	55	M	+	-	+	-	7	190	90	11.2	8	5.2	4.5	36	-	50	52	N	CKD	ND
70	40	F	-	+	-	-	6.2	110	110	3.2	8.2	4	4.8	39.3	-	45	16.6	N	CKD	D
71	57	F	+	+	-	-	9	160	210	9	7.8	6	6	46.8	+	48	6.1	N	CKD	ND
72	70	M	-	+	+	+	10	140	78	2.3	10	5.4	5.5	55	-	52	21.9	C	CKD	ND
73	60	M	-	+	+	-	8	126	90	3	9	4.5	4.8	43.2	+	45	16.6	N	CKD	ND
74	65	F	-	-	-	-	7.4	108	65	1.9	9.4	4	5	47	+	60	27.9	N	CKD	D
75	40	F	+	+	-	-	9	210	94	2.7	9.1	4.7	4.5	40.95	-	44	19.2	N	CKD	ND
76	60	M	+	+	-	-	8	170	160	7.2	8	5.6	5.2	41.6	+	48	7.4	N	CKD	ND
77	66	F	-	+	-	-	10	96	104	3.5	9.4	5	5	47	+	58	17	N	CKD	D
78	68	M	-	+	-	-	10	120	140	7.8	8	5.7	5.8	46.4	+	55	7	N	CKD	D
79	70	F	-	+	-	+	4	90	110	4.2	8.9	5	4.8	42.72	+	47	9.24	N	CKD	ND
80	35	F	-	-	-	-	12	120	90	1.9	10	4	4	40	-	62	35.3	N	CKD	D
81	60	M	+	+	-	-	11	220	140	5	8.2	4.8	4.6	37.72	+	50	11.1	N	CKD	ND
82	48	M	-	+	-	-	9.6	100	118	2.2	9.3	4.5	4.8	44.6	-	57	33.1	N	CKD	D
83	55	F	-	+	-	-	8	90	134	2.7	9.5	4.4	4.3	40.85	+	54	20.06	N	CKD	D
84	62	F	-	+	-	-	9	84	180	4.3	9.8	4.2	5.7	55.8	+	46	9.85	C	CKD	ND
85	70	M	-	+	+	-	10	100	120	3	9	5.1	5.2	46.8	-	48	11.5	N	CKD	ND
86	62	M	+	+	-	-	11	140	200	6	8.1	5	5.7	44.3	+	52	9.38	N	CKD	ND
87	59	M	+	+	-	-	7.2	140	80	6	10	5.5	5	50	+	50	9.3	N	CKD	D
88	44	M	-	+	-	-	10	88	74	1.7	9.6	3.8	4	38.4	-	60	47.05	N	CKD	ND
89	52	M	-	+	-	-	8	90	96	3	8.8	4	3.9	34.32	-	58	23.6	N	CKD	D
90	48	M	-	+	+	-	10	100	96	5.4	8.6	5.5	4.3	36.98	+	50	11.8	N	CKD	ND
91	40	M	-	+	-	-	6	110	110	2.5	9.1	4.8	4.7	42.77	+	58	32.2	N	CKD	D
92	50	F	+	+	-	-	7.1	104	150	3.2	8.5	4.6	5.5	46.7	+	47	15.6	C	CKD	ND
93	64	F	-	+	-	-	8	130	110	4	8.6	4.5	4.7	40.42	+	55	14.5	N	CKD	D
94	60	M	-	+	-	-	10	96	88	2.2	9.3	4.8	4.3	39.99	-	51	25.75	N	CKD	ND
95	40	M	-	+	-	-	11	130	80	2.5	9.6	5	5	48	+	55	30	N	CKD	D
96	38	M	-	-	-	-	11.5	124	70	2	9.8	4.6	4	39.2	-	60	42.2	N	CKD	ND
97	40	M	-	+	+		10	148	110	4.5	8.9	5	4.8	42.72	+	66	20.3	N	CKD	ND
98	65	F	-	+	-	+	8	80	95	3	9.1	4.8	5	45.5	+	55	16.23	N	CKD	ND
99	38	M	-	+	+	-	10	98	85	2.5	9	5	4.1	36.9	+	65	36.8	N	CKD	D
100	58	F	-	+	-	-	9	120	75	4.5	8.5	4.7	4.2	35.7	+	50	10.75	N	CKD	ND
101	40	M	+	+	+	+	9	110	114	4	8.8	4.2	4	35.2	-	60	20.8	N	CKD	ND
102	45	M	-	+	-	-	12.5	135	120	5.5	9	5	5	45	+	70	16.79	N	CKD	ND

NO	AGE	SEX	DM	HTN	CAD	CVA	Hb	RBS	Ur	Cr	Ca	K	P	Ca x P	Ur alb	Weight	Egfr	Echo	USG	DIALYSIS
1	54	M	-	-	-	-	13	80	24	0.8	9	4	3.2	28.8	-	55	82	N	N	ND
2	41	M	-	+	-	-	12.5	110	20	0.7	9.5	4.2	3.4	32.3	-	45	88	N	N	ND
3	38	F	+	-	+	-	12	88	22	1	10	4.5	3	30	+	55	67	N	N	ND
4	28	M	-	-	-	-	14	90	18	1.2	10.2	3.8	4	40.8	-	60	77.7	N	N	ND
5	58	M	-	+	+	-	13	118	24	1.2	8.8	5	3.5	30.8	-	65	65	N	N	ND
6	51	F	-	-	-	-	10	120	30	1	9	4.8	2.9	26.1	-	65	76	N	N	ND
7	48	M	-	-	-	-	12	84	28	1.1	9.5	4.4	3	28.5	-	58	68	N	N	ND
8	41	F	-	-	-	-	12.5	90	30	1	10	4	3.5	35	-	55	64	N	N	ND
9	34	M	-	-	-	-	15	110	20	1.2	8.9	3.8	3.5	31.15	-	68	83	N	N	ND
10	65	M	+	-	+	+	13	114	22	0.9	11	5	4	44	-	70	81	N	N	ND
11	49	M	-	-	-	-	12	78	26	0.8	10.3	3.6	3	30.9	-	68	107	N	N	ND
12	62	M	-	+	-	-	11.5	64	18	1	9.6	4	2.5	24	-	75	81	N	N	ND
13	58	F	+	-	-	-	9	130	22	0.8	8.6	4.2	2.6	22.3	+	50	61	N	N	ND
14	28	M	-	-	-	-	14	86	16	1.2	10	4.3	3	30	-	55	71.2	N	N	ND
15	44	M	-	-	-	-	13	90	20	1.1	10.5	4	3.2	33.6	-	60	72.7	N	N	ND
16	68	F	-	-	-	+	11	120	18	0.9	9	4.6	2.9	26.1	-	70	66	N	N	ND
17	58	M	+	-	+	-	12	128	20	0.8	8.8	4.4	3.5	30.8	-	55	78.2	N	N	ND
18	53	M	-	+	-	-	13	80	22	0.9	9	5	3.8	34.2	-	50	67	N	N	ND
19	39	F	-	-	-	-	12	98	18	0.8	10	3.6	3	30	-	50	74.5	N	N	ND
20	38	M	-	-	-	-	15	88	24	1	8.6	4	3	25.8	-	65	92	N	N	ND
21	41	M	-	-	+	-	14	108	20	1.2	9.3	4.6	2.5	23.25	-	70	80.2	N	N	ND
22	68	M	-	+	-	-	13.5	76	24	1	9	5	2.8	25.2	-	65	65	N	N	ND
23	54	M	-	-	-	-	13	80	18	0.9	10.2	5.1	2.7	27.5	-	~~60~~	79.6	N	N	ND
24	65	F	-	-	-	+	11	92	28	1	9.5	3.5	3	28.5	-	65	62	N	N	ND
25	39	M	-	-	+	-	13	100	24	0.8	8.8	4	2.6	22.88	-	70	120	N	N	ND
26	48	M	+	-	-	-	13.5	90	20	1	10	4.5	3	30	-	50	64	N	N	ND
27	55	F	-	+	-	-	10	88	24	1	10.3	4.8	3.1	31.9	-	65	65.2	N	N	ND
28	43	F	-	-	-	-	8	140	28	1.1	9.5	4	3.2	30.4	-	70	64	N	N	ND
29	30	M	-	-	-	-	13	106	20	0.8	9.6	4.2	3	28.8	-	60	114	N	N	ND
30	70	F	-	-	+	-	9	110	36	0.8	10.4	4.8	2.8	29.1	-	72	74.3	N	N	ND
31	59	M	-	+	-	-	11	78	24	1	10	4	3	30	-	63	70	N	N	ND
32	55	F	-	-	-	-	8	90	30	1.2	9	4.8	3.5	31.5	-	68	66.8	N	N	ND
33	45	M	+	-	+	-	11.5	100	26	1.1	8.8	4	4	35.2	+	60	71.9	N	N	ND
34	59	F	-	+	-	-	10	108	28	0.9	9.6	4.3	3.6	34.5	-	64	80	N	N	ND
35	60	M	-	-	-	-	12	98	28	1	10.1	4.1	3	30.3	-	69	65.1	N	N	ND
36	38	M	-	-	-	-	13	130	20	0.9	9.2	4.2	3.6	33.1	-	63	99.1	N	N	ND
37	52	M	+	-	-	-	10	104	26	0.8	8.6	4.5	3	25.8	-	55	84	N	N	ND
38	36	F	-	-	-	-	13	78	18	1	8.2	4	3.1	25.4	-	58	73.6	N	N	ND
39	65	F	-	-	-	-	11	80	26	1.1	9.5	3.8	4.1	38.9	-	75	60.3	N	N	ND
40	36	M	-	-	-	-	14	114	16	1	10	4	4	40	-	48	69	N	N	ND
41	42	F	+	-	-	-	11.5	128	20	0.8	9.6	3.5	3	28.8	-	68	98	N	N	ND
42	62	F	-	+	-	-	12	150	36	0.8	10.1	5	3.5	35.35	-	65	75	N	N	ND
43	36	M	-	-	-	-	13.5	90	18	1	9.5	3.8	3.6	34.2	-	60	86	N	N	ND
44	72	F	+	-	-	-	8	100	30	0.9	8.9	4.2	4.3	38.27	-	70	62	N	N	ND
45	53	F	-	-	-	-	10	88	24	1	9.4	4	4	37.6	-	60	62	N	N	ND
46	28	F	-	-	-	-	12	118	16	0.7	10	4.5	2.9	29	-	58	109.5	N	N	ND
47	55	M	+	-	+	-	10	86	20	1	9.8	5	3	29.4	-	60	70.8	N	N	ND
48	68	F	+	-	-	-	11	90	26	0.9	10.4	3.5	4	41.6	-	72	68	C	N	ND
49	48	F	-	-	-	-	7	88	25	1	10	4.6	3.1	31	-	70	76	N	N	ND
50	54	M	-	+	+	-	12.5	96	28	1	8.8	4.4	3	26.4	-	60	71.6	N	N	ND

NO	AGE	SEX	DM	HTN	CAD	CVA	Hb	RBS	UREA	CREATININE	Ca	POTASSIUM	P	Ca x P	Ur. Albumin	Weight	Egfr	Echo	USG	DIALYSIS
51	42	M	-	-	-	-	12	90	18	1	9	4	3.8	34.2	-	60	81	N	N	ND
52	55	M	-	-	+	-	11	78	20	1.1	9.2	4.5	4	36.8	-	58	62	N	N	ND
53	35	M	-	-	-	-	12	80	22	0.8	10	4.6	2.8	28	-	70	125	N	N	ND
54	44	M	+	-	-	-	11	110	16	0.9	9.6	3.8	3.5	33.6	+	65	96	N	N	ND
55	52	F	-	-	-	-	13	120	26	1	9.5	5	3.4	32.3	-	68	70	N	N	ND
56	28	M	-	-	-	-	10	90	20	0.9	8.8	4.1	2.5	22	-	65	112	N	N	ND
57	62	M	-	-	-	-	11	96	28	1	9	3.9	4.1	36.9	-	58	63	N	N	ND
58	48	M	+	-	+	-	12	88	30	0.9	8.6	3.8	4	34.4	-	60	76	N	N	ND
59	58	M	-	+	-	-	13	78	18	0.8	10.1	4	4.1	41.41	-	62	88	N	N	ND
60	36	M	-	-	-	-	14.5	120	20	0.9	9.8	4.2	3	29.4	-	65	104	N	N	ND
61	65	M	-	-	-	+	12	108	22	1	9.6	4.2	3.7	35.52	-	65	67.7	N	N	ND
62	44	M	-	-	+	-	12.4	98	26	1	9	4.6	3	27	-	63	84	N	N	ND
63	48	F	+	-	-	-	9	88	18	0.9	10	4.8	4	40	-	70	85	N	N	ND
64	36	M	-	-	-	-	13.5	80	16	1	9	3.8	3	27	-	73	105	N	N	ND
65	54	M	-	-	-	-	11	96	28	1.1	9.3	4	3.2	29.7	-	70	76	N	N	ND
66	73	M	-	-	+	-	12.5	114	20	1	9.5	3.7	4	38	-	65	60.5	N	N	ND
67	27	F	-	-	-	-	13	110	24	0.9	8.9	4.9	3	26.7	-	58	100	N	N	ND
68	55	M	-	+	-	-	10	98	30	1.1	10	4.2	3.8	38	-	60	64	N	N	ND
69	47	M	-	-	-	-	12	80	28	1.1	9.8	4.6	3.7	36.26	-	58	68	N	N	ND
70	55	M	-	+	-	-	11	90	20	0.8	9	4.3	3	27	-	55	81	N	N	ND
71	58	F	-	-	+	+	9	96	18	1	9.5	4	4	38	-	65	65	N	N	ND
72	66	M	-	+	-	-	10.5	104	28	0.8	8.9	4.1	3.5	31.15	+	55	70	N	N	ND
73	53	M	+	-	-	-	13	114	16	0.9	8.6	4.5	3.7	31.8	-	60	80	N	N	ND
74	36	F	-	-	-	-	12	90	30	0.8	10	4.4	4	40	-	60	92	N	N	ND
75	41	M	-	-	+	-	13	80	26	0.7	9.5	4.2	3.5	33.25	-	58	110	N	N	ND
76	62	M	-	+	-	+	11.5	120	22	0.9	8.9	4	3	26.7	-	60	72	N	N	ND
77	65	F	+	-	-	-	10	130	28	0.9	9.2	3.8	3.5	32.2	+	65	64	N	N	ND
78	56	M	-	-	+	-	13	132	20	1.1	9.9	3.8	4	39.6	-	60	64	N	N	ND
79	45	F	-	-	-	-	8	98	18	0.8	9.4	4.6	2.8	26.3	-	62	102	N	N	ND
80	29	M	-	-	-	-	14	100	24	0.9	8.9	4.2	2.6	23.14	-	60	100	N	N	ND
81	58	M	+	+	+	-	12.3	104	28	1	10	4.6	3	30	+	70	79	N	N	ND
82	64	F	-	-	-	-	11	90	32	0.8	9.6	4	3	28.8	-	65	73	N	N	ND
83	50	M	-	-	-	-	13	116	20	1	10.3	3.9	3.4	34.1	-	58	72.5	N	N	ND
84	55	F	-	+	+	-	10	140	28	0.9	8.8	3.8	4	35.2	-	58	65	N	N	ND
85	44	F	+	-	-	-	11	128	18	1	8.2	4	3.8	31.16	-	60	68	N	N	ND
86	38	M	-	-	-	-	14.5	108	20	0.9	8.6	4.5	3	25.8	-	68	107	N	N	ND
87	68	M	-	+	-	-	10	80	20	1	8.8	4.1	4	35.2	-	65	65	N	N	ND
88	62	F	-	-	-	-	9	98	22	0.8	9.5	4.3	3.7	35.15	-	58	67	N	N	ND
89	56	M	-	+	-	-	12	128	30	0.8	9.6	4	3.5	33.6	-	50	73	N	N	ND
90	45	M	-	-	-	-	13.5	120	26	1.1	9	3.8	3.6	32.4	-	55	66	N	N	ND
91	61	M	+	-	-	-	13	90	20	1	10	4	3.8	38	-	63	69	N	N	ND
92	52	M	-	-	-	-	10	98	28	0.8	8.6	3.9	3	25.8	-	60	91	N	N	ND
93	35	F	-	-	-	-	12.5	140	28	0.9	8.8	4.6	3.2	28.16	-	58	80	N	N	ND
94	33	M	-	-	-	-	14	110	16	0.9	9	4	3	27	-	65	107	N	N	ND
95	42	F	-	-	-	-	11	94	22	1	9.5	3.8	3.5	33.25	-	63	73	N	N	ND
96	55	M	-	-	-	-	14	120	16	0.8	10	3.6	3	30	-	50	80	N	N	ND
97	54	F	+	+	-	-	12	104	28	0.8	8.8	3.8	3.5	29.4	+	58	73	N	N	ND
98	35	M	-	-	-	-	15	110	20	1	9	4	3	27	-	62	90	N	N	ND
99	54	M	-	-	-	+	11	120	30	1	9.4	4.1	3.4	31.96	-	60	70	N	N	ND
100	46	M	+	-	-	-	12.5	120	24	0.9	9.5	4.5	3	28.5	-	68	99	N	N	ND